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(54) Skin treatment compositions, process for their preparation, applicator containing these compositions and method for their application.

(57) A cosmetically acceptable composition for topical application to human skin to provide skin benefit comprises an hydroxylated carboxylic acid and a cosmetically acceptable vehicle other than water.

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TITLE MODIFIED
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SKIN TREATMENT COMPOSITIONS

The invention relates to skin treatment compositions and in particular to compositions which reduce the dryness or flakiness of skin and which can improve the suppleness or smoothness of skin.

- 5 A soft, supple and flexible skin has a marked cosmetic appeal and is an attribute of normal functioning epidermis. The outer layer of the epidermis, i.e. the stratum corneum, can, however, become dry and flaky following exposure to adverse climatic conditions, or excessive contact with
- 10 detergents or solvents which result in loss of skin moisture, with the result that the skin loses its soft, supple and flexible characteristics. Emollients such as fats, phospholipids and sterols have in the past been used to soften dry skin, but it is apparent that these emollients are only partially effective as a remedy for this type of condition.

Also, topical application to the skin of classical humectants is unlikely to alleviate this problem since they are not particularly skin substantive and are generally rinsed from the skin during washing.

5 It is therefore evident that there exists a need for an effective treatment for skin which is in a dry, flaky condition and which is relatively inflexible.

As part of a programme to examine substances for their ability to improve skin condition, isolated guinea pig
10 footpad stratum corneum was selected as a test substrate and changes in its extensibility were measured after application of each test substance. The amount by which extensibility was increased was taken as a measure of the likely skin benefit that the substance might have on human
15 skin. The isolated guinea pig footpad stratum corneum was usually first 'damaged' by immersion in diethyl ether so that any benefit derived from subsequent treatment with a test substance could more readily be recognised. Of the many substances screened in this way, it was discovered
20 that, at low concentrations, certain hydroxylated carboxylic acids of medium chain length were effective in increasing the extensibility of solvent damaged guinea pig footpad stratum corneum while short and long chain hydroxylated carboxylic acids did not achieve this effect.

25 Following this initial discovery, it was subsequently confirmed by subjective assessment that the condition of human skin, particularly that which is in a dry, flaky and relatively inflexible condition, can be improved by topical application of such substances.

30 Accordingly, the invention provides a cosmetically acceptable composition for topical application comprising a skin benefit inducing amount of an hydroxylated carboxylic acid having from 4 to 12 carbon atoms in the molecule, together with a cosmetically acceptable vehicle other than
35 water.

The hydroxylated carboxylic acid

The likelihood of an hydroxylated carboxylic acid being capable of improving the condition of skin to which it is applied can first be assessed objectively by an in vitro method which involves measuring the change in extensibility of isolated stratum corneum to which the acid is applied. The technique employed will be described in detail later in the specification. A significant increase in extensibility can then be taken as an indicator that the acid, when applied to living human skin, is likely to improve the condition of that skin in terms of softness, suppleness and flexibility. Confirmation of this can be obtained by clinical studies which will also be described later.

Based on the results of these in vitro studies with isolated stratum corneum, it has been shown that the hydroxylated carboxylic acids for use in compositions according to the invention should have from 4 to 12 carbon atoms in the molecule, have one or more hydroxyl groups, are straight or branched chained and can be saturated or unsaturated.

Preferably, the carboxylic acid is a saturated acid with a single hydroxyl group in the α position. Examples are α -hydroxy-iso-butyric acid, α -hydroxy-iso-caproic acid, α -hydroxy-n-caproic acid, α -hydroxy-iso-caprylic acid, α -hydroxy-n-caprylic acid and α -hydroxy-n-capric acid.

Of these, the acid which produces the greatest increase in extensibility of the stratum corneum is α -hydroxy-n-caprylic acid.

Comparative measurements have shown that hydroxylated carboxylic acids having less than 4 carbon atoms or conversely more than 12 carbon atoms in the molecule, exhibit little or no increase in extensibility of stratum corneum when tested by the in vitro method to be described hereinafter.

It is furthermore apparent that the maximum benefit is obtained when the hydroxylated carboxylic acid is employed as the free acid rather than as a corresponding

salt or ester. The pH value of the composition is accordingly less than 7 and is usually from 2 to 4.

The amount of hydroxylated carboxylic acid employed is from 0.5 to 20%, preferably from 1 to 10% by weight of the composition. Expressed in terms of molar concentrations this is approximately equivalent to 0.01M to 1M, preferably 0.05M to 0.5M.

It should be explained that use of less than 0.5% of the hydroxylated carboxylic acid by weight of the composition is unlikely to confer on the user any noticeable skin benefit. The upper limits, on the other hand, are dictated more by the nature of the composition, i.e. solid or liquid, than by any limit of efficacy of the hydroxylated carboxylic acid as a skin benefit agent.

15 Cosmetically acceptable vehicle

The selection of a vehicle for hydroxylated carboxylic acids in the compositions of the invention presents a wide range of possibilities depending on the required product form of the composition. Suitable vehicles can be classified as described hereinafter.

It should be explained that vehicles are substances which can act as diluents, dispersants, or carriers for the hydroxylated carboxylic acids and which therefore ensure that they can be applied to and distributed evenly over the skin at an appropriate concentration; in certain cases, the vehicle can aid its penetration into the stratum corneum, thus ensuring that the effectiveness of the applied hydroxylated carboxylic acids are prolonged because of improved substantivity. It is not intended that water, which can act as a vehicle, is to be excluded; water can certainly be present in many of the compositions according to the invention, but it is intended that these compositions should contain at least one vehicle other than water.

35 The vehicles that can be used in compositions according to the invention can include solid, especially powdered

vehicles such as moisture absorbents, powdered binders and diluents and liquids such as emollients, propellants, solvents, humectants and thickeners. Examples of each of these types of vehicles, which can be used singly or as mixtures of one or more vehicles, are as follows:

Moisture absorbents

- Carragheenates
- Pectins
- Polyvinyl alcohol
- 10 Polyethylene oxides
- Polyvinylpyrrolidone
- Carboxyvinyl polymers
- Copolymers of methyl vinyl ether
- Maleic anhydrides
- 15 Mixed salts of calcium and sodium alginate
- Crosslinked dextrans
- Chemically modified cellulose
- Microcrystalline cellulose
- Calcium alginate
- 20 Alginic acid
- Pregelatinised starches
- Chemically modified starches
- Crosslinked starches
- 25 Starch copolymers such as hydrolysed (particularly base-hydrolysed) starch
- Polyacrylonitrile graft copolymers
- Crosslinked polyacrylamides
- Crosslinked polyacrylic acids
- Crosslinked polyhydroxyethyl methacrylate
- 30 Crosslinked polyvinyl alcohol
- Crosslinked polyvinylpyrrolidone
- Sulphonated polystyrene crosslinked with di-vinylbenzene
- 35 Quaternised polyvinyl pyridine crosslinked with di-vinyl benzene
- Magnesium silicate
- Lanolin absorption base
- Amorphous silica powder

Powder binders and diluents

- Microcrystalline cellulose
- Isostearyl neopentanoate
- Polyacrylamide
- 5 Lauryl lactate
- Precipitated silica
- Talc
- Chalk

Emollients

- 10 Stearyl alcohol
- Glyceryl monoricinoleate
- Glyceryl monostearate
- Sulphated tallow
- Propylene glycol
- 15 Mink oil
- Cetyl alcohol
- Stearyl stearate
- Isopropyl isostearate
- Dimethyl brassylate
- 20 Stearic acid
- Isobutyl palmitate
- Isocetyl stearate
- Oleyl alcohol
- Isopropyl laurate
- 25 Hexyl laurate
- Decyl oleate
- Di-isopropyl adipate
- 2-octadecanol
- Iso-cetyl alcohol
- 30 Myristyl ethoxymyristate
- Cetyl palmitate
- Dimethylpolysiloxane
- Di-isopropyl adipate
- Di-n-butyl sebacate
- 35 Di-isopropyl sebacate
- Di-2-ethyl hexyl sebacate

	2-ethyl hexyl palmitate
	Isononyl isononanoate
	Isodecyl isononanoate
	Isotridecyl isononanoate
5	2-ethyl hexyl palmitate
	2-ethyl hexyl stearate
	Di-(2-ethyl hexyl) adipate
	Di-(2-ethyl hexyl) succinate
	Isopropyl myristate
10	Isopropyl palmitate
	Isopropyl stearate
	Butyl stearate
	Glyceryl monostearate
	Polyethylene glycol
15	Propylene glycol
	Triethylene glycol
	Lanolin
	Castor oil
	Acetylated lanolin alcohols
20	Acetylated lanolin
	Petrolatum
	Isopropyl ester of lanolin fatty acids
	Mineral oils
	Butyl myristate
25	Isostearic acid
	Palmitic acid
	Isopropyl linoleate
	Cetyl lactate
	Lauryl lactate
30	Myristyl lactate
	Quaternised hydroxy alkyl aminogluconate
	Decyl oleate
	Isodecyl oleate
	Di-isopropyl adipate
35	2-ethyl hexyl palmitate
	Isostearyl neopentanoate

- Myristyl myristate
Di-isopropyl adipate
Oleyl ethoxy myristate
Diglycol stearate
5 Ethylene glycol monostearate
Myristyl stearate
Isopropyl lanolate

Propellants

- 10 Trichlorofluoromethane
Dichlorodifluoromethane
Dichlorotetrafluoroethane
Monochlorodifluoromethane
Trichlorotrifluoroethane
Propane
15 Butane
Isobutane
Dimethyl ether
Carbon dioxide

Solvents

- 20 Ethyl alcohol
2-ethyl hexanol
Ethylene carbonate
Propylene carbonate
Methylene chloride
25 Isopropyl alcohol
Castor oil
Linear ethoxylated polymer of methanol
Ethylene glycol monoethyl ether
Diethylene glycol monobutyl ether
30 Diethylene glycol monoethyl ether
Propoxylated butanol
Propoxylated oleyl alcohol
Butyl stearate
Butyl myristate

Humectants

- Glycerin
- Sorbitol
- Sodium 2-pyrrolidone-5-carboxylate
- 5 Soluble collagen
- Dibutyl phthalate
- Gelatin
- Polyglycerogen
- Ethoxylated (10-20 moles) glucose
- 10 Propoxylated (10-20 moles) glucose

Thickeners

- Gums
- Starch
- Colloidal silicon dioxide
- 15 Sodium polyacrylate
- Tetra alkyl and/or trialkyl aryl ammonium smectites
- Chemically modified magnesium aluminium silicate
- Organically modified montmorillonite clay
- Hydrated aluminium silicate
- 20 Fumed silica
- Carboxyvinyl polymer
- Sodium carboxymethyl cellulose
- Hydroxyethyl stearate amide
- Ethylene glycol monostearate

- 25 The quantity of vehicle employed can constitute the balance of the product, or a smaller proportion than the balance, provided that the vehicle, or mixture of vehicles, is capable of performing its function as herein defined.

- The vehicle, including water if present, will
- 30 accordingly comprise up to 99.5%, preferably from 80 to 99% by weight of the composition. The vehicle other than water will comprise at least 1%, preferably at least 10% by weight of the composition.

- The composition according to the invention can contain
- 35 ingredients other than those already mentioned, depending on the form of the intended product. It is, for example,

possible to include moisturisers, sunscreen agents, anti-septics or preservatives, antioxidants, anti-caking agents, emulsifiers, perfumes and colouring agents. Examples of some of the ingredients are as follows:

5 Moisturisers

Sodium pyrrolidone carboxylate

Sodium lactate

Orotic acid

Sunscreen Agents

10 p-aminobenzoic acid

Ethylene glycol salicylate

Propoxylated (2 moles) ethyl p-aminobenzoate

Dipropylene glycol salicylate

2-ethoxyethyl-p-methoxy cinnamate

15 Cetyl stearyl alcohol

2-hydroxy-4-methoxybenzophenone-5-sulphonic acid

Ethylhexyl-2-cyano-3,3-diphenyl acrylate

Urocanic acid

2-hydroxy-4-octyloxybenzophenone

20 Methyl-p-hydroxybenzoate

Homomenthyl salicylate

Antiseptics and preservatives

2-bromo-2-nitro propan-1,3-diol

Cetyl pyridinium chloride

25 3,4,4'-trichlorocarbaniide

2,4,4'-trichloro-2'-hydroxydiphenyl ether

Benzalkonium chloride

Para hydroxy benzoic acid

Dehydroacetic acid

30 Formaldehyde

EDTA

Antioxidants

Tocopherol

Ascorbyl palmitate

35 Propyl gallate

Butylated hydroxy toluene

Butylated hydroxyanisole

Anti-caking agents

Hydrophobic starch

Silicone dioxide

Anionic emulsifiers

5

Potassium stearate

Sodium stearate

Ammonium stearate

Triethanolamine stearate

10

Glyceryl monostearate containing either potassium
or sodium soap

Sodium lauryl sulphate

Sodium cetyl sulphate

Glyceryl monostearate containing sodium lauryl
sulphate

15

Cationic emulsifiers

N(stearoyl colamino formylmethyl) pyridinium chloride

N-soya-N-ethyl morpholinium ethosulphate

Alkyl dimethyl benzyl ammonium chloride

20

Di-isobutylphenoxyethoxyethyl dimethyl benzyl
ammonium chloride

Cetyl pyridinium chloride

Nonionic emulsifiers

25

Fatty acid esters of sorbitan anhydrides or ethylene
oxide products of sorbitan fatty acid esters such
as Span 80 or Tween 80; and pluronics which are
addition products of hydrophilic polyoxy ethylene
groups and a hydrophilic polyoxy propylene.The amount of emulsifiers, if used, usually form from
1 to 10%, preferably 1 to 5% by weight of the composition.

30

The benefit to the skin derived from topical
application of the composition can be assessed objectively
by measuring the increase in extensibility of isolated stratum
corneum following application of the composition to damaged
stratum corneum.

Measuring the extensibility of isolated stratum corneum

Stratum corneum is obtained from the rear feet of guinea pigs and prepared in a similar manner to that described by Middleton (1968) in Brit.J.Dermatol.80, 437.

5 The dissected footpads are incubated for 18 hours at 37°C in a solution of 0.5% (w/v) Trypsin (Koch-Light, ex Hog pancreas) and 2M urea dissolved in 0.1M tris (pH 7.4 HCl) and 0.02% (w/v) sodium azide. After digestion, the underlying tissues of dermis and lower layers of epidermis

10 are scraped away and the remaining transparent stratum corneum is washed twice in cold distilled water for two periods of two hours.

The samples of stratum corneum are kept in pairs throughout the experiment so that one of each pair acts

15 as a control.

Solvent damaged stratum corneum is prepared by immersing paired samples of stratum corneum in 10 ml diethyl ether (AR grade) at 25°C for 18 hours. After this treatment, the samples are washed in excess cold distilled

20 water to remove loosened fragments of stratum corneum cells adhering to the surface, and then immersed in 10 ml of cold distilled water for 15 hours with 3 changes of water to remove hygroscopic substances within the stratum corneum cells responsible for water binding.

25 Undamaged or solvent damaged samples of stratum corneum are thoroughly dried with filter paper after immersing in water and cut into rectangular strips 1.5 x 0.5 cm with a stainless steel punch. Control samples are washed in 10 ml of cold distilled water at

30 room temperature while the corresponding strips from the other footpads are immersed in 2 ml of the treatment solution under investigation. After 18 hours the pairs of stratum corneum are removed, dried with filter paper, transferred into labelled vials and placed in a humidifier

35 at 81% relative humidity using a saturated solution of potassium bromide. The stratum corneum samples are left to equilibrate at 81% RH for 10 days.

The extensibility of guinea pig stratum corneum is measured on an Instron Tester as described by Middleton (Supra). Pneumatic jaws, one serrated and one rubber pad, operate at a pressure of 15-20 psi inside a double walled perspex cabinet, in which air, circulated by a fan, is recycled through a saturated solution of potassium bromide. A wet and dry bulb hygrometer, positioned inside the cabinet, measures the enclosed humidity. Stratum corneum samples are handled with rubber gloves through ports in the cabinet. The lower jaw assembly and humidity cabinet remains fixed to the crosshead, whilst the upper jaw assembly connected to a 2kg load cell type B mounted on top of the crosshead, rises at a speed of 0.5 cms min^{-1} . The jaws are separated by a distance of 0.5 cm and the corneum strips are positioned between them. The extension cell is subjected to an increasing load as the strips are extended. This is recorded on a monitor, set at full scale deflection of 1kg force and a speed of 20 cms min^{-1} .

The extensibility of the stratum corneum strips is expressed as % extension/100g load, if necessary allowing for slack.

Individual experiments are performed on 20 samples of paired footpads. The sample mean is calculated for each set and mean differences between control and test extensibilities are analysed statistically by student t-tests to obtain significance levels.

Experiment

Extensibility measurements on undamaged and solvent damaged stratum corneum were carried out following treatment with solutions of α -hydroxy carboxylic acids according to the method described hereinbefore. The solutions employed were 0.15M aqueous solutions of the α -hydroxy acids at a pH value of from 2 to 3. The results obtained when using undamaged isolated stratum corneum showed that treatment with α -hydroxy caproic acid and with α -hydroxy caprylic acid induced a significant increase in extensibility. The results obtained

when using solvent damaged stratum corneum also indicated that a significant increase in extensibility was obtained following treatment with these acids. These latter results together with those obtained following treatment with other 5 α -hydroxy carboxylic acids are summarised in Table 1 below.

Extensibilities of solvent-damaged guinea pig footpads before and after treatment with various α -hydroxy carboxylic acids

5	0.15M aqueous solution of acid	pH	% extensibility/100g		Significance of difference (for 20 replicates)
			Control	Treated	
	lactic acid (C ₃)	2.35	1.40	1.75	0.35
	α-hydroxy-n-butyric (C ₄)	2.20	1.76	2.32	0.56
	α-hydroxy-iso-butyric (C ₄)	2.30	1.25	2.45	1.20
	α-hydroxy caproic (C ₆)	2.40	2.00	5.00	3.00
	α-hydroxy caprylic (C ₈)	2.40	1.64	8.42	6.78
	α-hydroxy capric (C ₁₀)	3.19	1.00	2.44	1.45

Saturated solutions of α -hydroxy lauric acid (C_{12}) and of α -hydroxy myristic acid (C_{14}), both of which had a pH of 7, were also tested in the same way using solvent damaged stratum corneum : there was however no significant difference in extensibility demonstrated between control and treated footpads for each of these acids probably because of their low solubility in water.

Otherwise, the tabulated results show a superiority for α -hydroxy-iso-butyric acid (C_4), α -hydroxy caproic acid (C_6) and α -hydroxy caprylic acid (C_8) as compared with an insignificant effect after treatment with both lactic acid (C_3) and α -hydroxy-n-butyric acid (C_4).

Product Forms

The compositions of the invention can be formulated as liquid, for example products such as lotions for use in conjunction with applicators such as a roll-ball applicator or a spray device such as an aerosol can containing propellant or a container fitted with a pump to dispense the product. Alternatively, the compositions of the invention can be solid or semi-solid, for example powders, moulded sticks, creams or gels, for use in conjunction with an applicator such as a powder sifter or a stick applicator, or simply a tube or lidded jar.

The invention accordingly also provides a closed container containing a cosmetically acceptable composition as herein defined.

The invention further provides a process for preparing a cosmetically acceptable composition for topical application to human skin, which process comprises mixing an hydroxylated carboxylic acid having from 4 to 12 carbon atoms in the molecule, with a cosmetically acceptable vehicle other than water.

Compositions according to the invention are intended for topical application to human skin which is already in a dry, flaky or relatively inflexible condition or prophylactically to normal healthy skin to prevent or reduce deteriorative changes of this sort.

The compositions are of particular benefit if applied to exposed skin areas during cold weather, or during exposure to strong sunlight sufficient to cause sunburn, or when the skin is exposed to repeated contact with
5 detergents or solvents. In each of these situations, the drying and tightening of the skin with subsequent breakdown to give flaking, peeling or cracking can be reduced or prevented with topical application to affected skin areas of compositions according to the invention.
10 The invention is illustrated by the following Examples of cosmetically acceptable compositions for topical application to human skin.

Example 1

This example illustrates an aerosol lotion which can
15 be prepared from the following ingredients.

	<u>% w/w</u>
Polyethylene glycol 1000 monostearate	2.4
Lanolin alcohols	1.0
Linear alcohol lactate	2.0
20 Myristyl myristate	1.5
Mineral oil 65/75	3.8
α -hydroxy caprylic acid (C_8)	2.0
Cationic detergent	1.0
Water	62.3
25 Alcohol	12.0
Propellant 12/114 (Dichlorodifluoromethane: dichlorofluoroethane - 40:60)	12.0

Example 2

This example illustrates a face cream which can be
30 prepared from the following ingredients, the oil phase and the aqueous phase being subsequently emulsified.

	i) <u>Oil phase</u>	<u>% w/w</u>
	Stearic acid	18.0
	Mineral oil	5.0
5	Polyoxyethylene (20) propylene glycol monostearate	5.0
	Propyl-p-hydroxy benzoate	0.05
	ii) <u>Aqueous phase</u>	<u>% w/w</u>
	Propylene glycol	5.0
	2-pyrrolidone-5-carboxylic acid	5.0
10	Sodium hydroxide	1.6
	α -hydroxy caprylic acid (C ₈)	2.0
	Triethanolamine	1.0
	Methyl-p-hydroxy benzoate	0.1
	Water	to 100

15

Example 3

This example illustrates a sunscreen cream which can be prepared by blending the following ingredients:

		<u>% w/w</u>
	Stearic acid	2
20	Wool alcohol	1
	Cetyl alcohol	3.5
	Polar wax, a polyoxyethylene ester of sorbitan	5
	Arachis oil	15
	Ethyl-p-dimethylaminobenzoate	0.75
25	Ethyl-p-diethylaminobenzene	0.75
	Butylated hydroxy toluene	0.02
	Glycerin	3
	Sodium citrate	0.05
	Methyl-p-hydroxybenzoate	0.1
30	Silicon fluid MS200	1
	Perfume oil	0.4 (v/w)
	α -hydroxy caproic acid (C ₆)	8
	Water	to 100

Example 4

This example illustrates a sunscreen lotion which can be prepared from the following ingredients:

	<u>% w/w</u>
5 Acetylated lanolin alcohols	5
2-ethoxyethyl-p-methoxycinnamate	2
α -hydroxy caprylic acid (C_8)	4
Isopropyl myristate	38
Mineral oil	to 100
10 Perfume	q.s.

Example 5

This example illustrates a suntan oil which can be prepared from the following ingredients:

	<u>% w/w</u>
15 Anhydrous lanolin	1
Non-volatile polymethylphenylsiloxane	1
Isopropyl palmitate	6
Homomenthyl salicylate	8
Perfume	0.2
20 α -hydroxy caproic acid (C_6)	3
Mineral oil	to 100

Example 6

This example illustrates a handcream which can be prepared by blending the following ingredients:

	<u>% w/w</u>
25 Isopropyl myristate	3.0
Polyethylene glycol (1000) monostearate	5.0
Stearic acid	19.0
Methyl paraben	0.15
30 Polyethylene glycol (300) monostearate	5.0
Sorbitol	3.0
α -hydroxy capric acid (C_{10})	1.0
Water	63.85
Perfume and colour	q.s.

Example 7

This example illustrates a lipstick which can be prepared by blending the following ingredients:

	<u>% w/w</u>
5 Carnauba wax	10.0
Beeswax	15.0
Lanolin	5.0
Cetyl alcohol	5.0
Castor oil	64.8
10 α -hydroxy-iso-butyric acid (C_4)	5.0

Example 8

This example illustrates an all-purpose mask which can be prepared by blending the following ingredients:

	<u>% w/w</u>
15 Kaolin	35.0
Bentonite	5.0
Cetyl alcohol	2.0
Sodium lauryl sulphate	1.0
Glycerin	10.0
20 Nipagin M	0.1
α -hydroxy caprylic acid (C_8)	5.0
Perfume	q.s.
Water	to 100

Example 9

25 This example illustrates a toothpaste which can be prepared from the following ingredients:

	<u>% w/w</u>
α -hydroxy caproic acid (C_6)	3.0
Aluminium hydroxide (microcrystalline)	41.5
Alumina (aluminium oxide)	2.0
5 Glycerol	28.0
Water	24.5
Sodium lauryl sulpho acetate	1.0
Flavour	0.7
Gum tragacanth	0.5
10 Methyl-p-hydroxybenzoate	0.1
Saccharin	0.05
Phosphoric acid to produce a pH of 6.5 to 7.5	q.s.

Example 10

This example illustrates a skin milk which can be
 15 prepared from the following ingredients:

	<u>% w/w</u>
Glyceryl monomyristate	3
Isopropyl isostearate	8
Oil	3
20 α -hydroxy capric acid (C_{10})	2
Carbopol 941	0.2
TEA	0.15
Water	to 100

Example 11

25 . This example illustrates a cream containing α -hydroxy caproic acid and its effect when applied to the human face during the winter months when exposure to cold weather was anticipated.

For the purposes of the human test, two creams were
 30 prepared - a test cream containing α -hydroxy caproic acid and a control cream containing no acid (cream base).

The cream base had the following formulation.

	<u>% w/w</u>
MYRJ 52 (polyoxyethylene 40-stearate)	1.0
CUTINA MD (ethylene glycol mono- and di-glyceride)	5.0
5 LANOL 14M (myristyl ethoxy myristate)	0.5
ALFOL 18RD (synthetic C ₁₈ alcohol)	1.0
CUTINA CP (cetyl palmitate)	2.5
NIPANOL M (propyl p-hydroxybenzoate)	0.1
NIPAGEN M (ethyl p-hydroxybenzoate)	0.2
10 Glycerol	3.0
RHODAPOL (heteropolysaccharides)	0.1
Water	86.6

15 α -hydroxy caproic acid, 4.0% w/w, was added to the cream base formulation and the pH adjusted to 3.5 by addition of sodium hydroxide to provide the test cream.

20 A panel of 54 female subjects was recruited for the test and each panellist was provided with both test and control creams. 0.2g of each cream was applied to each half face area twice daily under laboratory conditions and a tube of each cream was provided for similar use outside the laboratory. Faces were assessed in the laboratory by expert assessors for dryness and flakiness at the commencement of the test and twice a week for up to 4 weeks.

25 49 panellists completed the trial. Data for the whole trial period were examined using analysis of variance. A two-way product and subject analysis was carried out and the mean change in half-face score using the initial half-face score as co-variable was calculated.

30 The results indicated that the test cream induced a statistically significant improvement (>90% level) in the condition of the skin of the lower cheek during the test period.

Example 12

This example illustrates a cream containing α -hydroxy caproic acid and its effect when applied to the human hand, again during the winter months when exposure to cold weather was most likely to exacerbate skin problems.

For the purposes of the hand test, the test and control creams described in Example 11 were employed, except that they were unbuffered and had a pH of about 2.5.

A panel of 13 male and 37 female subjects was recruited for the test and each panellist was provided with both test and control creams.

Cream was applied to the backs of each hand, particularly to the finger webs, at least twice daily over a period of six weeks. The hands of the panel were assessed for skin dryness once a week during the clinical trial by expert assessors.

Statistical analysis of the accumulated data showed that at certain stages during the trial following exposure to particularly cold weather, the skin of the finger and thumb webs of the hand receiving the test cream were significantly less dry than the webs of the hand receiving the control cream, thus indicating that the α -hydroxy caproic acid had a benefitting effect on the skin. Improvements to the skin of hands receiving the test cream during periods of milder weather were not so marked.

It was, however, concluded from the results of both of the clinical trials described in Examples 11 and 12 that there was sufficient correlation between in vitro and in vivo (clinical) studies to predict from isolated stratum corneum extensibility data, the likelihood of skin benefit to the human subject following topical application of compositions of the invention.

Evidence for this latter conclusion can, for example, be derived from an examination of the in vitro data obtained when the test and control creams described in Example 11

were applied to isolated stratum corneum and the extensibility measured as hereinbefore described.

The data obtained are summarised in Table 2 below.

Table 2

The effect of α -hydroxy caproic acid in a cream base* on the extensibility of normal and solvent damaged guinea pig footpad stratum corneum

Substrate	pH	Control (c)	Test (t)	Difference	Standard Deviation of Difference	Significance level (20 replicates)
a) <u>Normal stratum corneum</u>						
c = base cream						
t = base cream + 0.3M acid	2.2	3.32	23.19	19.87	16.72	> 99%
	3.5	1.82	2.79	0.97	1.16	> 99%
b) <u>Solvent damaged stratum corneum</u>						
c = base cream						
t = base cream + 0.3M acid	2.2	2.55	15.49	12.96	7.32	> 99.9%
	3.5	1.77	3.17	1.40	1.25	> 99%
c = water						
t = base cream	7.0	0.93	1.18	0.25	1.04	Not significant

* as described in Example 11 with or without adjustment of pH.

It will be noted from this Table of results that the extensibility of isolated stratum corneum was significantly increased following treatment with a cream containing α -hydroxy caproic acid, compared with that following application of a control base cream which contained none of the acid. The significance of the increase was more dramatic with solvent damaged stratum corneum as the substrate, than with normal stratum corneum. A comparison of isolated solvent damaged stratum corneum treated with water versus cream base showed no significant increase in extensibility due to the cream base itself.

These in vitro results correlated well with the results of the corresponding in vivo tests using human subjects described in Examples 11 and 12.

CLAIMS:

1. A cosmetically acceptable composition for topical application, characterised in that it comprises a skin benefit inducing amount of an hydroxylated carboxylic acid having from 4 to 12 carbon atoms in the molecule, together with a cosmetically acceptable vehicle other than water.
2. A composition according to claim 1, characterised in that the hydroxylated carboxylic acid is an α -hydroxy carboxylic acid.
3. A composition according to claim 1 or 2, characterised in that the hydroxylated carboxylic acid is a saturated acid.
4. A composition according to claim 1,2 or 3, characterised in that the hydroxylated carboxylic acid has an unbranched carbon chain.
5. A composition according to any preceding claim, characterised in that the hydroxylated carboxylic acid is chosen from α -hydroxy-caproic acid, α -hydroxy caprylic acid, α -hydroxy-capric acid and mixtures thereof.
6. A composition according to claim 1,2 or 3, characterised in that the hydroxylated carboxylic acid has a branched carbon chain.
7. A composition according to any of claims 1,2,3 or 6, characterised in that the hydroxylated carboxylic acid is chosen from α -hydroxy-iso-butyric acid, α -hydroxy-iso-caproic acid and α -hydroxy-iso-caprylic acid and mixtures thereof.

8. A composition according to any of claims 1 to 7, characterised in that the hydroxylated carboxylic acid forms from 0.5 to 20% by weight of the composition.
9. A composition according to any preceding claim, in which the vehicle is chosen from powder absorbents, powder binders, powder carriers, emollients, propellants, solvents, humectants, thickeners and mixtures thereof.
10. A composition according to claim 12, in which the vehicle comprises up to 99.5% by weight of the composition.
11. A composition according to any preceding claim which is a cream, a lotion, a gel or a powder.
12. A process for preparing a composition according to any preceding claim, characterised in that it comprises forming a mixture of an hydroxylated carboxylic acid having from 4 to 12 carbon atoms in the molecule and a cosmetically acceptable vehicle other than water.
13. An applicator, characterised in that it contains the composition claimed in any of claims 1 to 11 and is suitable for dispensing the composition onto human skin.
14. A method of inducing skin benefit, characterised in that it comprises applying to the skin a skin benefit inducing amount of a composition according to any of claims 1 to 11.





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54 Skin treatment compositions, process for their preparation, applicator containing these compositions and method for
their application.

57 A cosmetically acceptable composition for topical ap-
plication to human skin to provide skin benefit comprises
an hydroxylated carboxylic acid and a cosmetically accept-
able vehicle other than water.

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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Inl. Cl. '1)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	<u>FR - A - 1 190 002</u> (WICKLEN PRO-DUCTS) * The abstract; page 1, column 1, paragraph 1 - page 2, column 1, paragraph 2; page 2, column 1, last paragraph - page 2, column 2, paragraph 1 *	1,3,5,6,7-14	A 61 K 7/48
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X	<u>US - A - 3 984 566</u> (E.J. VAN SCOTT) * The abstract; the claims 1-3 *	1-4,6-14	
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A	<u>DE - A - 2 401 752</u> (UNILEVER) * The claims *	1	
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A	<u>GB - A - 1 471 679</u> (AVON PRODUCTS) * The claims *	1	

			CATEGORY OF CITED DOCUMENTS
			X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons
			&: member of the same patent family. corresponding document
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
The Hague	14-11-1979	VANHECKE	